ORIGINAL RESEARCH

Animal farming and the risk of lymphohaematopoietic cancers: a meta-analysis of three cohort studies within the AGRICOH consortium

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ABSTRACT

Objective Animal farming entails a variety of potential exposures, including infectious agents, endotoxins and pesticides, which may play a role in the aetiology of lymphohaematopoietic cancers (LHCs). The aim of this study was to assess whether farming specific animal species is associated with the risk of overall LHC or its subtypes.

Methods Data from three prospective cohort studies in the USA, France and Norway which are part of the Agricultural Cohort consortium and which collected information about animal farming and cancer were used. Analyses included 316 270 farmers and farm workers. Adjusted Cox models were used to investigate the associations of 13 histological subtypes of LHC (n=3282) with self-reported livestock (cattle, pigs and sheep/goats) and poultry (ever/never and numbers raised) farming. Cohort-specific HRs were combined using random-effects meta-analysis.

Results Ever animal farming in general or farming specific animal species was not meta-associated with overall LHC. The risk of myeloid malignancies decreased with increasing number of livestock (p trend=0.01). Increased risk of myeloproliferative neoplasms was seen with increasing number of sheep/goats (p trend <0.01), while a decreased risk was seen with increasing number of livestock (p trend=0.02). Between cohorts, we observed heterogeneity in the association of type of animal farmed and various LHC subtypes.

Conclusions This large-scale study of three prospective agricultural cohorts showed no association between animal farming and LHC risk, but few associations between specific animal species and LHC subtypes were observed. The observed differences in associations by countries warrant further investigations.

Key messages

What is already known about this subject?

- Inconsistent associations between farming specific animal species and specific lymphohaematopoietic cancer subtypes in farmers have been reported in the literature.

What are the new findings?

- This is the first study to investigate the association between 13 histological subtypes of lymphohaematopoietic cancers and animal farming.
- The study found that the risk of myeloid malignancies and its subtypes decreased with greater numbers of livestock farmed.
- The study observed some differences in associations by countries that warrant further investigation of local farming conditions that may contribute to those effects.
- Furthermore, this work based on data from multiple studies allows investigation of rare cancer subtypes, but also permits comparisons across regions.

How might this impact on policy or clinical practice in the foreseeable future?

- These findings highlight the potential role of specific animal farming on the risk of specific lymphohaematopoietic cancer subtypes, indicating the need to research the aetiological causative or protective agents and their biological mechanisms.

INTRODUCTION

Farmers have lower overall cancer and mortality rates compared with the general population.[1–4] Nevertheless, the rates of certain cancers, including lymphohaematopoietic cancers (LHCs), have been reported to be higher among farmers.[5 6] Reasons for these elevated rates remain unclear, and may be due to a variety of exposures, including pesticides, allergens (eg, mites), endotoxins, bacteria and viruses.[7] Some studies have suggested that oncogenic viruses in poultry and livestock may be transmitted to humans and may be associated with increased risk of LHC in human.[8]

Inconsistent associations between exposure to specific animals and some LHC subtypes in farmers have been reported in the literature.[9–13] For instance, an increased risk of non-Hodgkin's lymphoma (NHL) was associated with contact with any cattle in the USA,[9 10] beef cattle in Canada[11] and livestock in China.[13] On the other hand, in Germany, there was an inverse association with NHL following contact with sheep, goats, rabbits

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and hares.[12] No association was found between NHL and contact with poultry.[11 12] Most of the previously conducted studies were limited by relatively small case numbers, which precluded examination of associations of other LHC or NHL subtypes. Because NHL subtypes demonstrate distinct genetic and epidemiological characteristics,[14] it is of great interest to consider associations within these strata. Furthermore, there may be heterogeneity in risk associated with the same animal species farmed across regions due to differences in population characteristics, agricultural practices and/or exposure patterns.[15]

The aim of the current analyses was to investigate whether farming specific animal species is associated with risk of overall LHC and LHC subtypes. We used data from three prospective agricultural cohorts which are part of the Agricultural Cohort (AGRICOH) consortium.[15] Combining data from large occupational cohorts of farmers documenting animal production in countries where animal husbandry is common made it possible to investigate associations of various types of animals with the risk of LHC subtypes. In addition, having data from three different countries allowed for investigation of heterogeneity of effects across countries.

METHODS

Study populations

AGRICOH is an international consortium of agricultural cohort studies established to examine the associations between health outcomes and agricultural exposures.[15] We used data from three prospective cohort studies that had relevant data available on animal production and cancer incidence, including the Agricultural Health Study (AHS)[16] from the USA, the AGRIculture and CANcer (AGRICAN) study[3] from France and the Cancer in the Norwegian Agricultural Population (CNAP) study[4] from Norway. A detailed summary of study design and participant details for this project, including inclusion criteria, has been published.[17]

Agricultural Health Study

The AHS includes 52 394 pesticide applicators with a private licence to apply restricted use pesticides (ie, farmers) in Iowa and North Carolina, USA.[16] Farmers were recruited and enrolled from 1993 to 1997 when they obtained or renewed their licences. At enrolment, participants were asked to report which of the following major income-producing animals were raised on the farm in the last year: beef and dairy cattle, pigs, sheep, poultry (including for eggs) and other animals. Farmers were also asked about the maximum number of livestock (<50, 50–99, 100–499, 500–999, ≥1000) and the maximum number of poultry (<50, 50–99, 100–499, 500–999, 1000–9999, ≥10 000) on their farm in the last year. For this analysis, we considered anyone who reported raising poultry or eggs for income as working with poultry and anyone reporting beef or dairy cattle, pigs, sheep or other livestock as working with livestock. Numbers of each specific livestock type were not collected at enrolment.

Subjects who had been diagnosed with cancer before the date of enrolment and those who did not live in either Iowa or North Carolina were excluded, leaving 51 167 farmers. Incident cases were identified through linkage to state cancer registries from the date of enrolment (1993–1997) to 31 December 2011 for Iowa and to 31 December 2010 for North Carolina.

AGRIculture and CANcer

AGRICAN includes 181 747 participants affiliated with the French agricultural health insurance scheme (Mutualité Sociale Agricole) for 3 years or more during their lifetime, including retired people, and living in one of the 11 geographical areas covered by a population-based cancer registry at the time of enrolment (1 November 2005–31 December 2007).[3] At enrolment, farmers and farm workers were asked if they had ever worked with each of the following types of animal: cattle, sheep or goat, pigs, horses, poultry and other animals. For each type of animal, they reported the tasks performed. These tasks included animal care, use of insecticides, milking, disinfection of milking equipment (for cattle and sheep/goats) and disinfection of barns (for cattle, sheep/goats, poultry and pigs). They reported the minimum and maximum numbers of each type of animal and the first and last year on which they performed each task. In this analysis, the number of each animal farmed was classified as the maximum number reported across all tasks and time periods. The number of livestock farmed was estimated by adding the maximum numbers of cattle, sheep/goat, pigs and horses. Participants were considered to have farmed dairy cattle if they reported cattle farming and milking and/or disinfection of milking equipment. No information was collected about farming beef cattle, specifically. This cohort collected information about farming sheep/goats, while the other two cohorts collected information about farming sheep only.

Subjects who were diagnosed with cancer before the date of enrolment, those with zero days of follow-up, and those who never worked on a farm or had incomplete information on agricultural status were excluded, leaving 127 282 farmers and farm workers. Incident cases were identified through linkage to cancer registries from the date of enrolment to 31 December 2009.

Cancer in the Norwegian Agricultural Population

CNAP includes 147 134 Norwegian farm holders. The cohort was constructed by linking data on farm characteristics and production from the compulsory agricultural censuses administered in 1969, 1979 and 1989, and horticultural censuses administered in 1974 and 1985 with the Central Population Register.[4] Farming specific animal species during the year preceding the census was collected through self-report, including the numbers of each of the following: beef and dairy cattle, pigs, sheep, chicken and other animals (horses, rabbits and fur animals). The numbers of animal species farmed were available as categorical variables (cattle: 0, 1–9, 10–19, 20–29, 30–49, ≥50; sheep or pigs: 0, 1–9, 10–19, 20–34, 35–49, 50–99, ≥100; chicken: 0, 1–99, 100–499, 500–999, 1000–1999, ≥2000). In this analysis, we used the maximum number of each specific animal reported by farm holders in any of the censuses. Since poultry other than chickens were not commonly farmed in Norway, information on other types was not collected, and the poultry variable represents chickens only. In CNAP, the total number of livestock farmed was unavailable.

In order to have a period of observation comparable with the other two cohorts, cancer follow-up started in 1993. Incident cases were identified by linking the agricultural census information on farm holders to the Norwegian Cancer Registry from 1993 to 2011. Farmers who died, emigrated or had a cancer diagnosis before the start of follow-up were excluded, leaving 137 821 farmers.

Cancer classification and follow-up

Incident LHC was coded by adopting the International Classification of Diseases for Oncology, Third Edition. Classifications for specific types and subtypes were coded according to the International Lymphoma Epidemiology Consortium[18] and Hematopoietic and Lymphoid Neoplasm Coding Manual from the Surveillance, Epidemiology, and End Results (SEER) programme.[19] We limited our analyses to 13 outcomes, including LHC overall (online supplementary table 1).

We censored follow-up at the date of diagnosis of the first incident cancer (except non-melanoma skin cancer in all cohorts and in situ bladder cancer in the AHS), date of death, date of migration out of study area or the end of follow-up, whichever occurred first.

Imputation

For AGRICAN, missing data on ever/never farming specific animal species and the number of each animal farmed were multiply imputed five times[20] and combined using Rubin's rules.[21] The percentage of missing data in AGRICAN was 15% for ever/never farmed a specific animal and 40%–60% for the number of animals. Because there were <5% missing data in AHS, data were not imputed; complete case analysis was used for this cohort. There were no missing data in CNAP.

Statistical analysis

HR and 95% CI were calculated using Cox proportional hazard models, with attained age as the time scale. The referent category consisted of farmers who did not farm the specific animal species being evaluated. For each type of animal (cattle, dairy cattle, beef cattle, pigs, sheep/goats, total livestock and poultry), we assessed associations with yes/no farming a specific type of animal and the number of each animal, categorised (cattle <30, 30+; sheep/goats and pigs <35, 35+; poultry and livestock <100, 100+). The cut points were selected by taking into consideration the cut points used in the CNAP census and the AHS questionnaire and to ensure that each category had at least five exposed cases for each LHC subtype in each cohort study. Due to the infrequency of farmers who farmed a very large number of animals (eg, ≥1000 poultry), we were not able to have more categories. Models were adjusted for sex in all three cohorts, state of residence in AHS and retirement status at enrolment in AGRICAN. We also controlled for exposure to pesticides that were associated with LHC in a previous AGRICOH pooling project.[22] For more details on the pesticides that we adjusted for, see footnotes of the respective tables. In brief, for CNAP and AHS, adjustment for individual pesticides was done using a cohort-specific fixed set of active ingredients, regardless of the lymphoma/myeloid type being modelled. The pesticides to adjust for in the set were identified, separately for each cohort, as those active ingredients (1) associated with a given lymphoid/myeloid malignancy on their own in minimally adjusted models and (2) not rarely used in the cohort population or in the country (ie, Norway). Lindane and dichlorodiphenyltrichloroethane (DDT) were also selected for inclusion as potential confounders because they were recently classified as carcinogenic and probably carcinogenic, respectively, by the International Agency for Research on Cancer Monograph programme on the identification of carcinogenic hazards to humans, with NHL being the site of most concern.[23] Tests for linear trend were conducted with the exposures coded as an ordinal variables. In some analyses for AGRICAN, the association between specific LHC subtypes and the number of specific animals farmed could not be calculated due to convergence issues.

We also carried out the following sensitivity analyses for yes/no variables: (1) using farmers who did not report farming any animals as the referent group; (2) examining the risk of LHC and its subtypes among farmers with single animal species versus no animals; and (3) restricting the analysis to reflect only the exposure experienced at the time of enrolment for AGRICAN and at the first time participating in the agricultural census for CNAP, to emulate the reference period for animal farming used in the AHS questionnaire.

Cohort-specific risk estimates were pooled using random-effect meta-analysis. Heterogeneity across cohorts was assessed using the I^2 statistic. I^2 values less than 25%, 50% and 75% indicate low, medium and high heterogeneity, respectively.[24] We report meta-risk estimates and cohort-specific estimates for overall LHC and its subtypes.

All analyses were conducted using Stata V.12.

RESULTS

Characteristics of the study populations

A total of 316 270 farmers and farm workers were included in this analysis, with 3282 LHC incident cases observed in 1993–2011. The characteristics of the cohorts are reported in table 1. The median age at the start of cancer follow-up was 67 years for farmers and farm workers in AGRICAN; this is 16–20 years older than the median age of the other two cohorts, due to the enrolment of retired farmers and farm workers. In AHS, 64% of participants reported farming any animal in the past year, while 84% and 74% in AGRICAN and CNAP ever worked with farm animals in their lifetimes, respectively. The most common type of animal farmed was cattle. Overall, AGRICAN had the highest prevalence of cattle, pig and poultry farming, while CNAP had the highest prevalence of sheep/goat farming. Whereas 50% of AGRICAN participants reported ever working with poultry, only 9% and 27% of AHS and CNAP participants farmed poultry, respectively. The numbers of specific animals farmed varied between the three cohorts. For example, of those who reported farming cattle, most of the farmers in AGRICAN reported farming 30 or more cattle, while most of the farmers in CNAP reported farming fewer than 30 cattle. However, when we restricted animal farming to reflect only the exposure experienced at the time of enrolment for AGRICAN and CNAP to emulate the reference period for animal farming used in the AHS, AGRICAN had the lowest prevalence of farming any animal species (data not shown). This may be attributed to the presence of retired farmers (51%) in this cohort.

The number of LHC cases varied between cohorts, with CNAP having the highest number (n=1968) and AGRICAN having the lowest number (n=632). Overall, lymphoid malignancies were more common than myeloid malignancies (n=2545, 78%; and n=737, 22%, respectively) (online supplementary table 1).

LHC and animal farming

The meta-associations between ever animal farming or ever farming specific animal species with overall LHC were close to the null (table 2). We observed significant association within specific cohorts with the number of animals farmed that were not observed in the meta-estimates. In AGRICAN, a lower risk of LHC was observed among farmers who farmed <35 sheep/goats (HR=0.82; 95% CI 0.70 to 0.97; p trend=0.05) and farmers who farmed <100 poultry (HR=0.77; 95% CI 0.63 to 0.95; p trend=0.76). Furthermore, in AGRICAN, the risk of LHC appeared to decrease with increasing number of pigs (p trend=0.05). In CNAP, a significantly increased risk of LHC was observed among farmers who farmed poultry (HR=1.12; 95% CI 1.01 to 1.23) and the risk increased with increasing number of poultry (p trend=0.01) (table 2).

Table 1 Characteristics of the three prospective agricultural cohort's studies included in this study (N=316 270)

	AGRICAN, France (n=127 282)	CNAP, Norway (n=137 821)	AHS, USA (n=51 167)
Median age at the start of follow-up (years)	67	51	46
Median (minimum–maximum) duration of cancer follow-up	3.4 years (1 day–4.6 years)	17.5 years (14 days–20.4 years)	14.7 years (1 day–18.0 years)
Gender (%)			
Male	56	84	97
Animal farmed (%)			
Any animal	84	74	64
Cattle	78	53	41
<30	24	42	–
30+	53	11	–
Dairy cattle	63	46	6
Beef cattle	–	39	37
Pigs	41	31	32
<35	29	25	–
35+	12	6	–
Sheep/goats*	23	41	3
<35	11	23	–
35+	12	18	–
Poultry†	50	27	9
<100	34	21	4
100+	16	6	4
Missing	0	0	1
Livestock‡	82	73	62
<100	50	–	19
100+	30	–	39
Missing	0	–	4
Retirement status at enrolment (%)			
Yes	51	–	–
No	49	–	–
Proportion classified as pesticide users (%)	68	63	99
State	–	–	
Iowa	–	–	61
North Carolina	–	–	39

*In AHS and CNAP, only sheep were reported. In AGRICAN, farmers reported farming sheep or goats but did not distinguish between the two.
†In CNAP poultry represents chicken farming only.
‡Livestock include cattle, pigs, sheep/goats and other animals.
–, not applicable for this cohort or not collected by this cohort; AGRICAN, AGRIculture and CANcer; AHS, Agricultural Health Study; CNAP, Cancer in the Norwegian Agricultural Population.

Myeloid malignancies and animal farming

We observed no meta-association between ever farming any animal or specific animal species and myeloid malignancies or its histological subtypes (table 3). Based on AGRICAN and AHS combined HR estimates, the meta-risks of myeloid malignancies and of subtypes myeloproliferative neoplasms (MPNs) and acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS) decreased with increasing number of livestock. In particular, in farmers who farmed 100 or more livestock, the risk of myeloid malignancies (meta-HR=0.66; 95% CI 0.48 to 0.90; p trend=0.01) and the risk of MPNs (meta-HR=0.50; 95% CI 0.29 to 0.86; p trend=0.02) were significantly lower. A lower risk of MPNs was also observed among farmers who farmed 30 or more cattle (meta-HR=0.44; 95% CI 0.18 to 1.06; p trend=0.02), while the risk of MPNs was significantly elevated among farmers who farmed 35 or more sheep/goats (meta-HR=2.34; 95% CI 1.25 to 4.38; p trend <0.01) based on the combined estimates from AGRICAN and CNAP. These meta-estimates were based on two cohorts as the number of livestock and specific animal species farmed were collected by only two cohorts.

There were some differences in the results between the individual cohorts. In CNAP, a lower risk of MPNs was observed among farmers who farmed beef cattle (HR=0.53; 95% CI 0.34 to 0.82), while a higher risk of AML/MDS was observed among farmers who farmed any animal (HR=1.35; 95% CI 1.05 to 1.44). In AHS, a lower risk of myeloid malignancies overall (HR=0.68; 95% CI 0.48 to 0.95) and of AML/MDS (HR=0.68; 95% CI 0.48 to 0.95) was observed among farmers who farmed any animal (table 4). In terms of the number of specific animals farmed, no significant associations were observed that are unique to individual cohorts (online supplementary tables 2–4).

Lymphoid malignancies and animal farming

Ever farming animals or specific animal species was not associated with the risk of lymphoid malignancies overall or their subtypes based on meta-estimates. We found an inverse association between lymphoid malignancies, NHL and NHL B cell type and farming less than 35 pigs (table 5). The risk of lymphoid malignancy subtypes varied between cohorts for the different animals farmed. In CNAP, an elevated risk of lymphoplasmacytic lymphoma/Waldenstrom was observed among farmers who farmed poultry (HR=1.55; 95% CI 0.99 to 2.42) (table 4), and the risk increased with increasing number of poultry farmed (p trend=0.02) (online supplementary table 4). An increased risk of follicular lymphoma (FL) was evident among cattle farmers in CNAP (HR=1.61; 95% CI 1.08 to 2.41), with the association retained in dairy cattle farming (HR=1.53; 95% CI 1.03 to 2.27) (table 4). In AGRICAN, the risk of lymphoid malignancies (HR=0.80; 95% CI 0.66 to 0.97; p trend=0.05), NHL (HR=0.79; 95% CI 0.66 to 0.96; p trend=0.03) and NHL B cell type (HR=0.77; 95% CI 0.63 to 0.94; p trend=0.01) was lower among farmers who farmed less than 35 sheep/goats (online supplementary table 2). The risk of marginal zone lymphoma (MZL) was increased with dairy cattle farming in AGRICAN (HR=19.95; 95% CI 1.21 to 99.10) (table 4). Furthermore, in AGRICAN, a lower risk of lymphoid malignancies (HR=0.77; 95% CI 0.59 to 0.99; p trend=0.52), NHL (HR=0.76; 95% CI 0.59 to 0.98; p trend=0.49) and NHL B cell type (HR=0.75; 95 CI 0.56 to 0.99; p trend=0.59) was observed among farmers who farmed less 100 poultry (online supplementary table 4). In AHS the risk of diffuse large B cell lymphoma (DLBCL) and multiple myeloma/plasma cell leukaemia was higher among farmers who farmed poultry (HR=1.78; 95% CI 1.05 to 3.04) and farmers who farmed sheep (HR=3.54; 95% CI 1.68 to 7.46), respectively (table 4). In AHS, an increased risk of lymphoid malignancies (HR=1.55; 95% CI 1.05 to 2.28; p trend=0.85), and in particular NHL and DLBCL, was observed among farmers who have farmed less than 100 poultry (online supplementary table 4).

Sensitivity analysis

When the referent group was those who did not farm any animal, the risk of FL increased with cattle farming (meta-HR=1.42; 95% CI 0.99 to 2.04), and this increase was still elevated in both

Table 2 Cohort-specific and meta-HR for the association between animal farming and the risk of overall LHC

	AGRICAN			CNAP			AHS			Meta			
	n	HR*	95% CI	n	HR†	95% CI	n	HR‡	95% CI	n	HR	95% CI	I^2
Any animal	564	1.15	0.95 to 1.41	1443	0.98	0.89 to 1.09	409	1.05	0.90 to 1.22	2416	1.03	0.95 to 1.11	5.3
Cattle	526	0.99	0.78 to 1.25	1008	1.00	0.91 to 1.09	270	1.04	0.89 to 1.21	1804	1.01	0.93 to 1.08	0.0
Number of cattle													
<30	172	0.91	0.72 to 1.15	792	0.98	0.89 to 1.08	–	–	–	964	0.97	0.89 to 1.06	0.0
30+	354	1.02	0.74 to 1.41	216	1.06	0.91 to 1.23	–	–	–	570	1.05	0.92 to 1.21	0.0
P trend			0.99			0.71	–	–	–			0.73	
Dairy cattle	425	1.04	0.87 to 1.25	864	0.99	0.90 to 1.08	31	1.01	0.70 to 1.45	1320	1.00	0.92 to 1.08	0.0
Beef cattle	–	–	–	740	1.00	0.91 to 1.10	247	1.02	0.87 to 1.19	987	1.00	0.93 to 1.09	0.0
Sheep/Goat	134	0.75	0.56 to 1.01	781	0.96	0.88 to 1.05	24	1.20	0.80 to 1.81	805	0.93	0.77 to 1.13	47.4
Number of sheep/goats													
<35	78	**0.82**	**0.70 to 0.97**	438	0.94	0.85 to 1.05	–	–	–	516	0.89	0.78 to 1.02	46.7
35+	57	1.00	0.62 to 1.61	343	0.98	0.87 to 1.10	–	–	–	400	0.98	0.87 to 1.10	0.0
P trend			**0.05**			0.54	–	–	–			0.30	
Pigs	289	0.84	0.71 to 1.00	580	0.95	0.86 to 1.04	194	1.14	0.96 to 1.35	1063	0.97	0.83 to 1.12	67.9
Number of pigs													
<35	205	0.88	0.74 to 1.04	440	0.90	0.81 to 1.00	–	–	–	645	0.89	0.83 to 1.12	0.0
35+	83	0.64	0.36 to 1.11	140	1.14	0.96 to 1.36	–	–	–	233	0.91	0.52 to 1.59	73.6
P trend			**0.05**			0.91	–	–	–			0.39	
Poultry	344	0.89	0.73 to 1.08	552	**1.12**	**1.01 to 1.23**	60	1.04	0.80 to 1.36	956	1.03	0.88 to 1.19	53.3
Number of poultry													
<100	223	**0.77**	**0.63 to 0.95**	412	1.08	0.96 to 1.20	30	1.31	0.91 to 1.89	665	1.00	0.77 to 1.31	79.2
100+	121	1.16	0.85 to 1.58	140	**1.25**	**1.05 to 1.49**	17	0.75	0.46 to 1.21	278	1.11	0.87 to 1.42	49.4
P trend			0.76			**0.01**			0.65			0.06	
Livestock	552	1.10	0.91 to 1.33	1414	0.99	0.89 to 1.09	395	1.04	0.89 to 1.21	2361	1.02	0.94 to 1.10	0.0
Number of livestock													
<100	344	0.83	0.52 to 1.31	–	–	–	122	0.89	0.72 to 1.10	466	0.88	0.73 to 1.07	0.0
100+	204	0.95	0.73 to 1.24	–	–	–	248	1.16	0.97 to 1.38	452	1.08	0.89 to 1.30	11.3
P trend			0.87	–	–	–			0.13			0.24	

*HR: AGRICAN: Cox regression adjusted for sex, retirement status, tobacco and pesticide use on crops.
†HR: CNAP, myeloid neoplasms: Cox regression adjusted for sex, aldicarb, lindane, dichlorodiphenyltrichloroethane (DDT) and mancozeb; HR: CNAP, lymphoid neoplasms: Cox regression adjusted for sex, dichlorvos, aldicarb, lindane, DDT, deltamethrin, mancozeb, linuron and glyphosate.
‡HR: AHS, myeloid neoplasms: Cox regression adjusted for sex, state, tobacco, chlorpyrifos, terbufos, dichlorvos, dicamba, glyphosate, lindane, DDT, aldicarb and captan; HR: AHS, lymphoid neoplasms: Cox regression adjusted for sex, state, tobacco, terbufos, lindane, DDT, permethrin, dicamba, parathion and carbaryl.
–, not collected by this cohort; AGRICAN, AGRIculture and CANcer; AHS, Agricultural Health Study; CNAP, Cancer in the Norwegian Agricultural Population; LHC, lymphohaematopoietic cancer; n, number of exposed cases. Values in bold are statistically significant at the 5% level

beef and dairy cattle farming (data not shown). Furthermore, the risk of FL increased with cattle farming (meta-HR=1.54; 95% CI 1.05 to 2.26), when we restricted the analysis to exposure during the year of enrolment. The risk of FL was also elevated among farmers who only farmed cattle versus no animal farmed (meta-HR=1.85; 95% CI 1.18 to 2.90).

There was little change from the main analysis for the other estimates when we considered the referent group to be those farmers with no animal exposure, examined the risk among farmers who farmed only one specific animal species or when we restricted the analysis to exposure during the year of enrolment (data not shown).

DISCUSSION

In this meta-analysis of three agricultural cohorts, we observed no meta-association between ever animal farming and the risk of LHC overall. Subtype-specific analyses also showed no meta-associations with the main subgroups of lymphoid malignancies, except for a significantly elevated risk of FL among cattle farmers in the sensitivity analysis. The risk of myeloid malignancies and its subtypes decreased with greater numbers of livestock. For MPNs, the direction of the association depended on the type and number of animal produced. The risk decreased with an increasing number of cattle, while the risk increased with an increasing number of sheep/goats. Within the three cohorts, we observed some difference in risk between specific types of animal farmed and some LHC subtypes. Ever animal farming was associated with a lower risk of myeloid malignancies and AML/MDS in AHS, but it was associated with increased risk of AML/MDS in CNAP. Farming sheep was associated with an increased risk of DLBCL in AHS. In AGRICAN, farming fewer sheep/goats was associated with a lower risk of LHC, lymphoid malignancies, NHL and NHL B cell. In CNAP, the risk of FL was increased with cattle farming, while the risk of MPNs decreased with beef farming. Farming dairy cattle was associated with an increased risk of MZL in AGRICAN. Farming poultry increased the risk of LHC and DLBCL in CNAP and AHS, respectively. The risk of LHC and lymphoplasmacytic lymphoma/Waldenstrom increased with increasing number of poultry farmed in CNAP. Farming fewer poultry was associated with a lower risk of LHC, lymphoid malignancies, NHL and NHL B cell in AGRICAN, but it was associated with an increased risk of lymphoid malignancies and in particular NHL in AHS. The risk of LHC decreased with an increasing number of pigs in AGRICAN.

Table 3 Meta-association between animal farming and myeloid malignancies, overall and by subtypes

	Myeloid malignancies				Acute myeloid leukaemia/myelodysplastic syndromes				Myeloproliferative neoplasms			
	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2
Any animal	537	0.91	0.68 to 1.22	62.9	329	0.85	0.58 to 1.50	63.5	150	0.97	0.63 to 1.50	38.1
Cattle	401	0.88	0.73 to 1.06	15.6	257	0.94	0.74 to 1.18	10.1	105	0.77	0.57 to 1.04	0.0
Number of cattle												
<30	226	0.89	0.61 to 1.31	65.8	144	1.03	0.80 to 1.33	0.0	57	0.72	0.37 to 1.38	67.2
30+	122	0.72	0.51 to 1.01	0.0	84	0.94	0.63 to 1.41	0.0	33	0.44	0.18 to 1.06	33.1
P trend			0.15				0.95				**0.02**	
Dairy cattle	303	0.98	0.82 to 1.16	0.0	195	1.07	0.85 to 1.34	0.0	80	0.88	0.63 to 1.23	0.0
Beef cattle	196	0.88	0.73 to 1.06	0.0	123	0.95	0.69 to 1.33	39.3	44	0.69	0.37 to 1.27	57.1
Sheep/Goats	213	0.97	0.65 to 1.45	66.3	118	0.91	0.71 to 1.15	0.0	71	1.32	0.67 to 2.59	65.3
Number of sheep/goats												
<35	124	1.02	0.78 to 1.34	48.4	73	No conv	No conv	No conv	36	1.31	0.79 to 2.17	49.2
35+	89	1.14	0.88 to 1.47	0.0	45	No conv	No conv	No conv	35	**2.34**	**1.25 to 4.38**	37.1
P trend			0.47								**<0.01**	
Pigs	242	0.89	0.73 to 1.09	16.7	163	0.95	0.73 to 1.24	20.7	58	0.76	0.54 to 1.09	0.0
Number of pigs												
<35	163	0.91	0.70 to 1.19	43.8	114	0.98	0.69 to 1.40	52.9	40	0.85	0.60 to 1.22	0.0
35+	44	0.94	0.64 to 1.39	0.0	28	1.01	0.61 to 1.64	0.0	12	0.72	0.33 to 1.59	0.0
P trend			0.48				0.87				0.27	
Poultry	230	0.91	0.61 to 1.37	71.4	153	1.03	0.72 to 1.45	45.3	60	1.10	0.78 to 1.56	0.0
Number of poultry												
<100	167	0.94	0.63 to 1.42	60.8	110	0.98	0.66 to 1.45	39.7	44	1.10	0.75 to 1.62	0.0
100+	61	1.03	0.72 to 1.48	26.8	42	1.15	0.81 to 1.63	0.0	16	1.08	0.61 to 1.93	0.0
P trend			0.87				0.66				0.62	
Livestock	523	0.92	0.73 to 1.15	43.0	319	0.84	0.61 to 1.17	52.8	147	1.01	0.70 to 1.46	19.3
Number of livestock												
<100	130	0.85	0.59 to 1.22	0.0	92	0.90	0.35 to 2.30	68.1	25	0.58	0.16 to 2.18	41.7
100+	92	**0.66**	**0.48 to 0.90**	0.0	54	0.72	0.48 to 1.08	0.0	31	**0.50**	**0.29 to 0.86**	0.0
P trend			**0.01**				**0.04**				**0.02**	

*AHS adjusted for sex, state, chlorpyrifos, terbufos, dichlorvos, dicamba, glyphosate, lindane,dichlorodiphenyltrichloroethane (DDT), aldicarb and captan; AGRICAN adjusted for sex, retirement status and number of crops for which farmer/worker personally applied pesticides; CNAP adjusted for sex, aldicarb, lindane, DDT and mancozeb.
AGRICAN, AGRIculture and CANcer; AHS, Agricultural Health Study; CNAP, Cancer in the Norwegian Agricultural Population; n, number of exposed cases; no conv, model did not converge in AGRICAN. Values in bold are statistically significant at the 5% level.

Epidemiological studies of lymphoid malignancies in association with animal farming have produced conflicting results. Similarly, this study found inconsistent results between lymphoid malignancy subtypes and farming specific animal species between cohorts. For instance, a statistically elevated risk of multiple myeloma was observed among sheep farmers in the AHS but not among sheep/goat farmers in AGRICAN and CNAP. An excess risk of multiple myeloma among participants who worked with sheep has been reported in previous findings,[25 26] including in a previous analysis within AHS,[27] while other studies found no association.[28]

We observed no meta-association between ever farming any of the animal species and NHL, which is similar to some individual studies,[9 29 30] although others have reported a decreased risk of NHL among farmers who had contact with cattle[31] and sheep/goats,[12] and increased risk of NHL among farmers who farmed beef cattle.[11] In a previous publication by AHS, an increased risk of NHL with ever poultry farming (relative risk=1.6; 95% CI 1.0 to 2.4) was observed, while in the current study this association was slightly attenuated (HR=1.21; 95% CI 0.90 to 1.63). The observed difference may be attributed to the longer follow-up and the inclusion of female farmers in this present study and also to the different variables adjusted in the models.[27]

In our study, we found an elevated risk of FL among farmers who farmed cattle when other referent groups were used. Notably, the HR for NHL overall was 1.00, that is, the other subtypes compensated the effect seen in FL. A population-based, case–control study in the San Francisco Bay area found a non-significantly elevated risk of FL among workers who reported working with cattle (OR=1.5; 95% CI 0.73 to 3.1).[9] The increased risk of FL could be due to an oncogenic virus such as bovine leukaemia virus, which is known to cause bovine leukaemia/lymphoma of B cells.[32] Moreover, it could be related to some other factors associated with raising cattle, such as the use of insecticides. For instance, the AHS found an elevated risk of FL among pesticide applicators who reported high use of diazinon, carbaryl and lindane.[33] In the current study we adjusted for specific pesticides (including carbaryl and lindane but not diazinon) identified in another AGRICOH analysis[22]; however, this adjustment did not substantially modify the estimates.

We found some inverse relationships in myeloid malignancies and its subtypes with increasing number of livestock. Furthermore, we observed a decrease in risk of some of LHC subtypes, within the specific cohorts. Exposure to allergens derived from animals has been reported to increase the risk of allergic diseases,[34 35] which may, in turn, affect the risk of developing cancer. It has been suggested that allergies increase the capacity of the immune system to recognise and remove pathogens and other foreign bodies, including transformed cells, resulting in

Table 4 Association between farming any animal or specific animal species and the risk of LHC subtypes, by cohort

	Any animal									Cattle								
	AGRICAN			CNAP			AHS			AGRICAN			CNAP			AHS		
	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
Myeloid malignancies	153	0.96	0.67 to 1.38	304	1.10	0.87 to 1.40	80	**0.68**	**0.48 to 0.95**	142	0.74	0.50 to 1.10	206	0.99	0.80 to 1.22	53	0.78	0.55 to 1.09
MPN	41	0.87	0.47 to 1.61	89	1.36	0.84 to 2.20	20	0.65	0.33 to 1.31	36	0.53	0.28 to 1.01	54	0.83	0.56 to 1.23	15	0.93	0.47 to 1.83
AML and MDS	34	0.70	0.35 to 1.42	176	**1.35**	**1.05 to 1.44**	43	**0.56**	**0.36 to 0.87**	103	0.90	0.52 to 1.55	125	1.06	0.81 to 1.40	29	0.71	0.45 to 1.12
Lymphoid malignancies	411	1.24	0.98 to 1.58	1139	0.92	0.82 to 1.04	329	1.10	0.91 to 1.33	384	1.12	0.84 to 1.48	802	0.97	0.87 to 1.08	217	1.07	0.89 to 1.27
NHL	399	1.28	1.00 to 1.64	1087	0.92	0.81 to 1.04	307	1.10	0.90 to 1.33	373	1.14	0.86 to 1.51	764	0.97	0.87 to 1.08	204	1.07	0.89 to 1.29
NHL B cell	359	1.29	0.99 to 1.67	1012	0.92	0.81 to 1.04	288	1.08	0.88 to 1.31	337	1.14	0.83 to 1.55	714	0.97	0.87 to 1.09	194	1.09	0.90 to 1.32
CLL/SLL	83	1.15	0.68 to 1.92	199	0.86	0.65 to 1.14	74	0.90	0.62 to 1.32	78	0.96	0.54 to 1.72	133	0.86	0.66 to 1.10	50	0.96	0.67 to 1.39
Lymphoplasmacytic lymphoma	34	1.25	0.55 to 2.86	70	1.06	0.62 to 1.80	3	–	–	32	1.04	0.42 to 2.57	51	1.07	0.68 to 1.69	1	–	–
DLBCL	69	1.52	0.81 to 2.83	177	0.93	0.69 to 1.25	71	1.24	0.82 to 1.86	63	1.12	0.59 to 2.11	120	0.91	0.69 to 1.19	48	1.20	0.82 to 1.77
MZL	27	3.71	0.87 to 15.81	32	1.07	0.52 to 2.21	9	1.14	0.34 to 3.86	27	–	–	24	1.23	0.64 to 2.35	7	1.45	0.48 to 4.38
FL	29	1.09	0.47 to 2.54	93	1.37	0.85 to 2.21	43	1.25	0.72 to 2.19	26	0.61	0.26 to 1.40	74	**1.61**	**1.08 to 2.41**	32	1.50	0.91 to 2.49
Multiple myeloma/plasma cell leukaemia	94	1.09	0.67 to 1.78	258	0.90	0.71 to 1.15	51	0.90	0.59 to 1.38	89	1.18	0.62 to 2.26	191	1.10	0.88 to 1.38	31	0.81	0.52 to 1.25
NHL T cell	23	0.92	0.36 to 2.34	58	1.21	0.70 to 2.10	13	1.48	0.50 to 4.38	21	1.21	0.36 to 4.00	37	0.94	0.58 to 1.52	6	0.68	0.25 to 1.84

	Beef cattle						Dairy cattle								
	CNAP			AHS			AGRICAN			CNAP			AHS		
	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
Myeloid malignancies	146	0.91	0.73 to 1.13	50	0.81	0.58 to 1.14	122	1.05	0.76 to 1.46	175	0.96	0.78 to 1.18	6	0.80	0.35 to 1.83
MPN	30	**0.53**	**0.34 to 0.82**	14	0.99	0.50 to 1.96	32	0.85	0.47 to 1.54	48	0.89	0.60 to 1.33	1	–	–
AML and MDS	95	1.08	0.82 to 1.44	28	0.76	0.48 to 1.20	89	1.20	0.79 to 1.82	106	1.02	0.77 to 1.33	3	–	–
Lymphoid malignancies	594	0.97	0.87 to 1.09	197	1.03	0.86 to 1.23	302	1.03	0.83 to 1.28	689	0.97	0.87 to 1.07	25	1.01	0.67 to 1.51
NHL	564	0.96	0.85 to 1.08	158	1.03	0.86 to 1.25	293	1.04	0.83 to 1.29	657	0.96	0.86 to 1.08	23	1.00	0.65 to 1.52
NHL B cell	523	0.95	0.84 to 1.07	175	1.04	0.86 to 1.26	265	1.04	0.83 to 1.30	613	0.97	0.86 to 1.08	23	1.07	0.70 to 1.63
CLL/SLL	93	0.77	0.58 to 1.01	47	0.98	0.68 to 1.42	57	0.77	0.47 to 1.26	122	1.00	0.77 to 1.29	3	–	–
Lymphoplasmacytic lymphoma	42	1.26	0.79 to 2.00	0	–	–	23	0.84	0.43 to 1.66	41	0.89	0.57 to 1.40	1	–	–
DLBCL	88	0.90	0.68 to 1.28	42	1.09	0.74 to 1.61	49	1.06	0.63 to 1.80	105	0.95	0.73 to 1.25	6	1.14	0.50 to 2.62
MZL	15	0.86	0.43 to 1.73	6	1.20	0.40 to 3.61	26	**19.95**	**1.21 to 99.10**	19	0.99	0.51 to 1.89	2	–	–
FL	52	1.28	0.85 to 1.92	28	1.31	0.79 to 2.18	22	0.79	0.38 to 1.65	65	**1.53**	**1.03 to 2.27**	6	2.13	0.91 to 4.98
Multiple myeloma/plasma cell leukaemia	140	1.09	0.86 to 1.38	30	0.87	0.56 to 1.35	71	1.09	0.67 to 1.77	160	1.02	0.82 to 1.28	1	–	–
NHL T cell	30	1.17	0.71 to 1.94	6	0.80	0.29 to 2.16	17	1.10	0.39 to 3.14	34	1.08	0.67 to 1.75	0	–	–

	Sheep/Goats									Pigs								
	AGRICAN			CNAP			AHS			AGRICAN			CNAP			AHS		
	n	HR*	95% CI	n	HR†	95% CI	n	HR‡	95% CI	n	HR*	95% CI	n	HR†	95% CI	n	HR‡	95% CI
Myeloid malignancies	39	0.76	0.49 to 1.16	174	1.15	0.94 to 1.40	2	–	–	79	0.75	0.52 to 1.08	128	1.01	0.81 to 1.27	35	0.79	0.53 to 1.19
AML and MDS	27	0.73	0.43 to 1.23	70	0.96	0.74 to 1.26	1	–	–	60	0.77	0.48 to 1.24	82	1.14	0.85 to 1.52	21	0.80	0.48 to 1.36
MPN	11	0.87	0.42 to 1.78	60	**1.75**	**1.20 to 2.57**	1	–	–	18	0.68	0.30 to 1.52	33	0.87	0.56 to 1.35	7	0.53	0.22 to 1.26
Lymphoid malignancies	96	0.75	0.52 to 1.07	607	0.94	0.85 to 1.04	22	1.36	0.88 to 2.09	209	0.88	0.72 to 1.08	452	0.86	0.76 to 0.97	159	1.15	0.94 to 1.41
NHL	91	0.72	0.50 to 1.04	576	0.93	0.83 to 1.03	22	1.46	0.95 to 2.25	204	0.89	0.72 to 1.09	438	0.88	0.78 to 1.00	146	1.14	0.92 to 1.41
NHL B cell	82	0.72	0.51 to 1.02	543	0.95	0.85 to 1.06	21	1.48	0.95 to 2.31	181	0.87	0.70 to 1.08	410	0.88	0.78 to 1.00	136	1.12	0.90 to 1.40
CLL/SLL	21	0.82	0.45 to 1.51	102	0.94	0.73 to 1.21	4	–	–	49	1.16	0.72 to 1.86	88	0.91	0.69 to 1.21	40	1.20	0.80 to 1.80
Lymphoplasmacytic lymphoma	7	0.67	0.24 to 1.91	37	0.99	0.64 to 1.53	1	–	–	12	0.51	0.21 to 1.21	28	0.86	0.53 to 1.40	2	–	–
DLBCL	18	0.84	0.39 to 1.80	96	0.95	0.73 to 1.25	2	–	–	37	1.05	0.60 to 1.85	76	1.02	0.76 to 1.37	33	1.24	0.79 to 1.95
MZL	6	0.85	0.25 to 2.85	14	0.60	0.31 to 1.16	2	–	–	13	1.03	0.41 to 2.60	9	0.67	0.31 to 1.46	4	–	–
FL	3		–	46	0.93	0.63 to 1.36	1	–	–	11	0.45	0.20 to 1.06	37	0.99	0.65 to 1.51	17	0.80	0.44 to 1.46
Multiple myeloma/plasma cell leukaemia	21	0.70	0.42 to 1.16	142	0.96	0.77 to 1.19	8	**3.54**	**1.68 to 7.46**	50	0.89	0.56 to 1.41	99	0.84	0.66 to 1.08	26	1.39	0.84 to 2.29
NHL T cell	6	0.84	0.20 to 3.51	25	0.69	0.42 to 1.13	1	–	–	15	1.71	0.58 to 5.04	22	0.99	0.58 to 1.69	7	1.41	0.50 to 3.99

	Livestock									Poultry								
	AGRICAN			CNAP			AHS			AGRICAN			CNAP			AHS		
	n	HR*	95% CI	n	HR†	95% CI	n	HR‡	95% CI	n	HR*	95% CI	n	HR†	95% CI	n	HR‡	95% CI
Myeloid malignancies	149	0.95	0.67 to 1.34	259	1.06	0.84 to 1.34	79	0.72	0.51 to 1.00	99	0.81	0.58 to 1.14	123	1.24	0.99 to 1.54	8	0.58	0.29 to 1.19
AML and MDS	107	0.97	0.63 to 1.48	122	0.99	0.73 to 1.35	42	**0.58**	**0.37 to 0.92**	71	0.79	0.51 to 1.20	75	1.28	0.96 to 1.71	7	0.94	0.43 to 2.03
MPN	40	0.87	0.48 to 1.60	87	1.32	0.83 to 2.11	20	0.71	0.35 to 1.43	26	0.90	0.47 to 1.71	34	1.20	0.79 to 1.83	–	–	–
Lymphoid malignancies	403	1.17	0.93 to 1.47	1119	0.94	0.84 to 1.06	316	1.06	0.88 to 1.28	245	0.92	0.71 to 1.17	429	1.04	0.93 to 1.17	52	1.20	0.90 to 1.60
NHL	391	1.20	0.94 to 1.51	1068	0.94	0.94 to 1.06	296	1.07	0.88 to 1.30	238	0.91	0.72 to 1.17	408	1.04	0.92 to 1.17	49	1.21	0.90 to 1.63
NHL B cell	352	1.18	0.92 to 1.51	994	0.93	0.93 to 1.06	279	1.07	0.88 to 1.31	213	0.90	0.69 to 1.18	381	1.04	0.92 to 1.17	44	1.14	0.84 to 1.56
CLL/SLL	81	0.92	0.57 to 1.48	193	0.85	0.65 to 1.12	74	0.97	0.66 to 1.42	52	0.97	0.56 to 1.66	81	1.09	0.84 to 1.43	6	0.59	0.26 to 1.35
Lymphoplasmacytic lymphoma	34	1.37	0.60 to 3.14	69	1.09	0.65 to 1.84	3	–	–	14	0.48	0.22 to 1.02	34	1.55	0.99 to 2.42	1	–	–
DLBCL	68	1.50	0.82 to 2.75	175	0.97	0.72 to 1.30	67	1.14	0.76 to 1.71	39	0.95	0.55 to 1.63	66	1.07	0.80 to 1.43	16	**1.78**	**1.05 to 3.04**
MZL	27	4.15	0.97 to 17.68	31	1.00	0.49 to 2.04	9	1.21	0.36 to 4.13	19	2.08	0.67 to 6.44	12	1.23	0.62 to 2.44	1	–	–
FL	28	1.03	0.46 to 2.30	93	1.49	0.92 to 2.41	42	1.27	0.73 to 2.22	16	0.61	0.23 to 1.61	31	0.96	0.63 to 1.48	4	–	–
Multiple myeloma/plasma cell leukaemia	91	1.01	0.63 to 1.61	255	0.94	0.74 to 1.20	48	0.86	0.56 to 1.32	60	0.95	0.53 to 1.73	90	0.96	0.75 to 1.23	8	0.98	0.48 to 2.04
NHL T cell	23	1.00	0.39 to 2.56	57	1.22	0.71 to 2.09	12	1.20	0.42 to 3.39	16	1.48	0.57 to 3.86	22	1.23	0.74 to 2.06	3	–	–

*HR: AGRICAN: Cox regression adjusted for sex, retirement status and number of crops for which farmer/worker personally applied pesticides.
†HR: CNAP, myeloid malignancies: Cox regression adjusted for sex, aldicarb, lindane, dichlorodiphenyltrichloroethane (DDT) and mancozeb; HR: CNAP, lymphoid malignancies: Cox regression adjusted for sex, dichlorvos, aldicarb, lindane, DDT, deltamethrin, mancozeb, linuron and glyphosate.
‡HR: AHS, myeloid malignancies: Cox regression adjusted for sex, state, chlorpyrifos, terbufos, dichlorvos, dicamba, glyphosate, lindane, DDT, aldicarb and captan; HR: AHS, lymphoid malignancies: Cox regression adjusted for sex, state, terbufos, lindane, DDT, permethrin, dicamba, parathion and carbaryl.
–, <6 exposed cases or 0 non-exposed cases; AGRICAN, AGRIculture and CANcer; AHS, Agricultural Health Study; AML, acute myeloid leukaemia; CCL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; CNAP, Cancer in the Norwegian Agricultural Population; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; LHC, lymphohaematopoietic cancer; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MZL, marginal zone lymphoma; n, number of exposed cases; NHL, non Hodgkin's lymphoma. Values in bold are statistically significant at the 5% level.

Table 5 Meta-association between animal farming and lymphoid malignancies, overall and by subtypes

	Lymphoid malignancies				Non-Hodgkin's lymphoma				Non-Hodgkin's lymphoma, B cell				Chronic/Small lymphocytic leukaemia/lymphoma			
	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2
Any animal	1879	1.06	0.89 to 1.26	65.7	1659	1.06	0.88 to 1.29	69.0	1659	1.05	0.87 to 1.28	66.8	356	0.91	0.74 to 1.12	0.0
Cattle	1403	1.01	0.92 to 1.10	0.0	1245	1.01	0.92 to 1.10	0.0	1245	1.01	0.92 to 1.11	0.0	261	0.90	0.74 to 1.09	0.0
Number of cattle																
<30	738	0.96	0.86 to 1.06	0.0	706	0.95	0.86 to 1.06	0.0	657	0.96	0.86 to 1.06	0.0	117	0.79	0.62 to 1.01	0.0
30+	448	1.09	0.93 to 1.28	0.0	432	1.08	0.92 to 1.27	0.0	394	1.06	0.92 to 1.27	0.0	94	0.96	0.54 to 1.71	0.0
P trend			0.64				0.73				0.82				0.54	
Dairy cattle	1016	0.98	0.89 to 1.08	0.0	973	0.98	0.89 to 1.08	0.0	901	0.98	0.89 to 1.09	0.0	179	0.94	0.75 to 1.18	0.0
Beef cattle	791	0.99	0.90 to 1.09	0.0	749	0.98	0.89 to 1.08	0.0	698	0.97	0.88 to 1.08	0.0	140	0.84	0.66 to 1.06	9.7
Sheep/Goat	725	0.96	0.75 to 1.22	53.9	689	0.97	0.72 to 1.30	66.9	646	0.97	0.72 to 1.31	68.2	123	0.92	0.73 to 1.17	0.0
Number of sheep/goats																
<35	392	0.88	0.77 to 1.00	32.1	373	0.87	0.76 to 0.99	30.1	349	0.86	0.72 to 1.04	58.6	73	0.94	0.74 to 1.20	0.0
35+	311	0.96	0.84 to 1.10	0.0	294	0.94	0.82 to 1.08	0.0	276	0.96	0.83 to 1.11	0.0	50	0.87	0.62 to 1.22	0.0
P trend			0.25				0.21				0.29				0.34	
Pigs	820	0.94	0.79 to 1.12	66.8	788	0.95	0.82 to 1.11	55.3	727	0.94	0.81 to 1.09	48.6	177	1.03	0.83 to 1.26	0.0
Number of pigs																
<35	482	**0.85**	**0.79 to 0.97**	0.0	469	**0.86**	**0.77 to 0.96**	0.0	428	**0.85**	**0.76 to 0.95**	0.0	97	0.95	0.74 to 1.22	0.0
35+	179	0.82	0.44 to 1.54	67.7	173	0.84	0.46 to 1.54	65.3	162	0.83	0.42 to 1.67	69.8	40	1.08	0.70 to 1.67	0.0
P trend			0.06				0.12				0.19			0.34	0.95	
Poultry	726	1.04	0.96 to 1.15	0.0	638	1.03	0.93 to 1.15	3.3	638	1.05	0.92 to 1.14	0.0	139	1.02	0.81 to 1.28	0.0
Number of poultry																
<100	498	1.03	0.76 to 1.38	77.5	476	1.02	0.76 to 1.37	77.0	437	0.98	0.75 to 1.28	66.4	89	0.85	0.53 to 1.35	42.4
100+	217	1.13	0.95 to 1.34	0.0	192	1.13	0.95 to 1.35	0.0	192	1.12	0.93 to 1.34	0.0	48	1.18	0.80 to 1.74	0.0
P trend			0.21				0.21				0.29				0.55	
Livestock	1838	1.02	0.90 to 1.16	37.2	1755	1.04	0.90 to 1.19	46.4	1625	1.02	0.89 to 1.17	40.5	348	0.89	0.73 to 1.09	0.0
Number of livestock																
<100	336	0.88	0.70 to 1.10	0.0	326	0.89	0.70 to 1.12	0.0	299	0.89	0.70 to 1.14	0.0	63	0.67	0.40 to 1.12	0.0
100+	360	1.18	0.98 to 1.42	0.0	340	1.19	0.98 to 1.44	0.0	313	1.18	0.96 to 1.43	0.0	89	1.05	0.70 to 1.57	0.0
P trend			0.07				0.06				0.10				0.64	

	Lymphoplasmacytic lymphoma				Diffuse large B cell lymphoma				Marginal zone lymphoma				Follicular lymphoma				Multiple myeloma				Non-Hodgkin's lymphoma, T cell			
	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2
Any animal	104	1.11	0.71 to 1.74	0.0	317	1.10	0.84 to 1.44	21.4	68	1.36	0.71 to 2.60	14.3	165	1.28	0.92 to 1.79	0.0	403	0.93	0.77 to 1.13	0.0	94	1.18	0.76 to 1.82	0.0
Cattle	83	1.07	0.71 to 1.60	0.0	231	1.01	0.82 to 1.24	0.0	31	1.28	0.73 to 2.24	0.0	132	1.28	0.80 to 2.05	54.3	311	1.05	0.87 to 1.26	0.0	64	0.91	0.61 to 1.37	0.0
Number of cattle																								
<30	46	1.01	0.65 to 1.54	0.0	112	0.91	0.70 to 1.17	0.0	NA	NA	NA	NA	68	1.00	0.34 to 2.92	80.1	178	1.08	0.87 to 1.34	0.0	33	0.87	0.54 to 1.40	0.0
30+	37	1.38	0.76 to 2.50	0.0	71	0.97	0.64 to 1.45	0.0	NA	NA	NA	NA	31	1.30	0.65 to 2.60	18.1	102	1.41	0.89 to 2.23	29.3	25	1.50	0.76 to 2.93	0.0
P trend			0.42				0.64								0.71				0.20				0.54	
Dairy cattle	64	0.88	0.60 to 1.28	0.0	160	0.99	0.78 to 1.24	0.0	45	2.59	0.26 to 26.09	76.3	93	1.38	0.85 to 2.22	41.9	231	1.03	0.84 to 1.26	0.00	51	1.09	0.70 to 1.68	0.0
Beef cattle	NA	NA	NA	NA	130	0.96	0.76 to 1.21	0.0	21	0.95	0.52 to 1.71	0.0	80	1.29	0.94 to 1.77	0.0	170	1.04	0.84 to 1.28	0.00	36	1.08	0.69 to 1.70	0.0
Sheep/Goats	44	0.93	0.62 to 1.39	0.0	144	0.94	0.73 to 1.21	0.0	20	0.65	0.37 to 1.16	0.0	NA	NA	NA	NA	171	1.23	0.62 to 2.46	84.7	31	0.71	0.44 to 1.12	0.0

continued

Table 5 continued

	Lymphoplasmacytic lymphoma				Diffuse large B cell lymphoma				Marginal zone lymphoma				Follicular lymphoma				Multiple myeloma				Non-Hodgkin's lymphoma, T cell			
	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2	n	HR*	95% CI	I^2
Number of sheep/goats																								
<35	24	No conv	No conv	No conv	66	0.97	0.75 to 1.26	0.0	9	No conv	No conv	No conv	NA	NA	NA	NA	84	0.80	0.64 to 1.00	0.0	18	0.81	0.51 to 1.31	0.0
35+	21	No conv	No conv	No conv	48	0.93	0.66 to 1.32	0.0	11	No conv	No conv	No conv	NA	NA	NA	NA	79	1.12	0.86 to 1.47	0.0	13	0.70	0.36 to 1.35	0.0
P trend							0.67												0.76				0.22	
Pigs	40	0.75	0.48 to 1.18	8.4	146	1.08	0.86 to 1.35	0.0	22	0.80	0.44 to 1.45	0.0	65	0.81	0.55 to 1.18	23.2	175	0.96	0.73 to 1.26	35.0	44	1.15	0.74 to 1.78	0.0
Number of pigs																								
<35	27	No conv	No conv	No conv	81	0.99	0.76 to 1.30	0.0	9	No conv	No conv	No conv	NA	NA	NA	NA	113	0.85	0.68 to 1.07	0.0	29	1.15	0.71 to 1.84	0.0
35+	14	No conv	No conv	No conv	32	1.27	0.73 to 2.0	4.1	11	No conv	No conv	No conv	NA	NA	NA	NA	37	0.87	0.56 to 1.36	0.0	8	0.81	0.29 to 2.31	0.0
P trend							0.51								NA				0.20				0.93	
Poultry	48	0.90	0.28 to 2.83	85.4	121	1.18	0.85 to 1.64	40.2	31	1.41	0.78 to 2.54	0.0	47	0.90	0.61 to 1.32	0.0	158	0.96	0.78 to 1.20	0.0	38	1.28	0.82 to 2.02	0.0
Number of poultry																								
<100	29	0.72	0.18 to 2.86	80.4	81	1.26	0.65 to 2.47	78.4	20	1.20	0.61 to 2.36	0.0	35	0.89	0.53 to 1.48	12.5	116	0.97	0.76 to 1.24	0.0	26	1.18	0.72 to 1.96	0.0
100+	19	1.50	0.56 to 4.03	63.3	37	1.25	0.86 to 1.82	0.0	11	2.19	0.94 to 5.15	0.0	12	0.82	0.41 to 1.62	0.0	41	1.02	0.71 to 1.45	0.0	12	1.61	0.79 to 3.30	0.0
P trend			0.78				0.19				0.10				0.58				0.91				0.19	
Livestock	103	1.17	0.75 to 1.81	0.0	310	1.08	0.87 to 1.35	0.0	67	1.43	0.67 to 3.03	32.9	163	1.32	0.95 to 1.84	0.0	394	0.93	0.77 to 1.13	0.00	92	1.17	0.76 to 1.79	0.0
Number of livestock																								
<100	NA	NA	NA	NA	68	1.12	0.70 to 1.79	0.0	NA	NA	NA	NA	32	1.12	0.34 to 1.05	0.0	67	0.60	0.34 to 1.05	0.0	17	No conv	No conv	No conv
100+	NA	NA	NA	NA	60	1.19	0.76 to 1.85	0.0	NA	NA	NA	NA	34	0.93	0.70 to 1.64	0.0	68	1.07	0.70 to 1.64	0.0	18	No conv	No conv	No conv
P trend							0.39								0.75				0.75					

*AHS adjusted for sex, state, state, terbufos, lindane, DDT, permethrin, dicamba, parathion and carbaryl; AGRICAN adjusted for sex, retirement status and number of crops for which farmer/worker personally applied pesticides; CNAP adjusted for sex, dichlorvos, aldicarb, lindane, dichlorodiphenyltrichloroethane (DDT), deltamethrin, mancozeb, linuron and glyphosate.
AGRICAN, AGRIculture and CANcer; AHS, Agricultural Health Study; CNAP, Cancer in the Norwegian Agricultural Population; n, number of exposed cases; NA, not applicable as only one study contributed to this estimate; no conv, model did not converge in AGRICAN. Values in bold are statistically significant at the 5% level .

reduced cancer risk.[36] For instance, a study found an inverse associations between self-reported allergies and both myeloid and lymphoid malignancies among individuals living in rural residence, which were probably due to their contact with a variety of agriculture-specific exposures.[37] Another explanation for the reduced risk could be attributed to exposure to endotoxins, which are highly present in animal settings and have been suggested to have anticarcinogenic actions.[38] Hence, future studies should study the risk of cancer including LHC subtypes in relation to endotoxin exposure and the joint effects of allergies with animal farming.

In contrast, there were some increased risks observed for myeloid malignancies. For example, we observed an increased risk of MPNs among farmers who farmed 35 sheep/goats or more and the risk increased with increasing number. We are unaware of studies that have investigated the association between animal farming and MPNs. On the other hand, agricultural work has been shown to be associated with MPNs in some studies[39 40] but not all.[41] Therefore, more studies are needed to elucidate the role of animal farming on MPNs.

The difference in association observed between specific animal farming and LHC could be due to the differences in the production of given animal species and the type of exposures that occur when farming specific animal species. For instance, exposure to dust and endotoxin is much higher in poultry and pig farming than in cattle farming.[42 43] Farming different animal species may result in exposure to different bioaerosols,[44] which could cause various health effects including cancer.[45]

We observed some differences in the HR estimates for LHC subtypes between the cohorts, which could be due to the differences in population characteristics, lifestyle, farm characteristics, including different micro-organisms, follow-up period, duration of animal husbandry, age of cohort, type of data collected and time of exposure. For example, farmers in CNAP and AHS had a longer follow-up period than AGRICAN farmers. Exposure to animal farming was based on lifetime exposure in AGRICAN and CNAP, while for AHS it was based on exposure during the year prior to recruitment/enrolment. There could be other differences in agricultural practices between countries (eg, degree of confinement of animals, use of ventilation systems, use of protective gear, regulations and legislation of farming). In conclusion, there appears to be no universal association, and if there are specific causal associations underlying mechanisms are rather complex and not necessarily easily transferable across LHC types, populations and farming practices.

To our knowledge, this is the largest analysis to date that assessed the association between animal farming and the risk of LHC subtypes. A notable strength of this analysis is the inclusion of data from three large prospective studies from different geographical regions. The AHS has previously published findings in relation to animal farming and some LHC subtypes.[27] Our analysis of AHS data included more cases than that included in the previous publication because the follow-up time was longer and female farmers were included.[27] Another advantage of this study is the uniform definition of LHC subtypes.

Limitations include that we were unable to address the type of caring tasks performed with animals, the duration of animal farming or exposure during childhood. For AHS, exposures reflected only the year before enrolment and so we might have classified some farmers as unexposed who were in fact previously exposed. Furthermore, we were unable to determine potential specific aetiological agents; thus, it is unknown whether the observed association was related to exposure to animal viruses or microbes, a heightened immune response stimulated by farm-related exposures or some other factor, such as exposure to disinfectants applied to the animals or confinements. We also could not evaluate exposure lags or the impact of cessation of certain types of exposure, which has been important in other studies of animal farming and cancer.[46] In addition, farming animals was assessed in different ways across the cohorts and there was some difference in the number of animals farmed. Because of the prospective design, we expect any exposure misclassification to be non-differential with respect to case status, which may lead to attenuations of associations. Chance findings cannot be ruled out due to a large number of comparisons with multiple exposures we investigated.

In conclusion, for the most part, we did not observe evidence of meta-associations between ever animal farming and LHC risk. There was some indication of an inverse association between myeloid malignancies and its subtypes with an increasing number of livestock. Moreover there were some suggestions of increased risk of MPN with increasing number of sheep/goats and a decreased risk of MPN with increasing number of cattle. We also observed some differences in associations by countries that warrant further investigation.

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